



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY  
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HEALTH EFFECTS DIVISION  
SCIENTIFIC DATA REVIEWS  
EPA SERIES 361

OFFICE OF  
PREVENTION, PESTICIDES AND  
TOXIC SUBSTANCES

**MEMORANDUM**

DATE: 7-MAY-2008

SUBJECT: **Difenoconazole**; Section 18 Emergency Exemption For Use on Almonds in California.

<b>PC Code:</b>	128847	<b>DP Barcode:</b>	351715
<b>Decision No.:</b>	392318	<b>Registration No.:</b>	08CA12
<b>Petition No.:</b>	NA	<b>Regulatory Action:</b>	Section 18
<b>Risk Assessment Type:</b>	Single Chemical/Aggregate	<b>Case No.:</b>	NA
<b>TXR No.:</b>	NA	<b>CAS No.:</b>	119446-68-3
<b>MRID No.:</b>	NA	<b>40 CFR</b>	§180.475

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TO: Daniel Rosenblatt/Stacey Groce (PM, Team 05)  
RD; (7505P)

The California Department of Pesticide Regulation (DPR) has requested an emergency exemption for the use of fungicide difenoconazole [1-[2-[2-chloro-4-(4-chlorophenoxy)phenyl]-4-methyl-1,3-dioxolan-2-ylmethyl]-1H-1,2,4-triazole] in/on almond for control of *Alternaria* leaf

*Rec'd in PR @ 5/16/2008*

spot; this is the first time the request for a specific emergency exemption of use on almonds has been made. Inspire™ (23.2% flowable liquid; Reg. no.: 100-1262), containing difenoconazole as the active ingredient (ai), is to be applied to almonds at the rate of 0.11 pounds (lb) ai per acre (A) using ground equipment. Up to 2 applications for a total rate of 0.22 lb ai/A may be made, with a pre-harvest interval (PHI) of 30 days. The proposed use period is from April 15 to June 30, 2008. A summary of the estimated human-health risk resulting from the requested use of difenoconazole is provided in this document.

**Note:** HED completed a Section 3 risk assessment for the use of difenoconazole in/on fruiting vegetables, pome fruit, sugar beets, tuberous and corm vegetables, and imported papaya in November 2007 (Memo, Sahafeyan, *et al.*, 09-NOV-07; DP# 346591). This document contains only those aspects of the risk assessment which are affected by the addition of the proposed difenoconazole use on almonds.

**Conclusions/Recommendations:** HED concludes that the toxicological, residue chemistry, dietary (food + water) exposure, and occupational/residential exposure assessments are adequate to support Section 18 registration and time-limited tolerances for residues of difenoconazole, [1-[2-[2-chloro-4-(4-chlorophenoxy)phenyl]-4-methyl-1,3-dioxolan-2-ylmethyl]-1*H*-1,2,4-triazole] *per se* in/on the following commodities:

Almond.....	0.05 ppm
Almond, hulls.....	5.0 ppm

**Note to RD:** The current tolerance for beet, sugar, should be changed from 0.01 ppm to 0.30 ppm due to the error made in the executive summary part of the previous risk assessment (M. Sahafeyan, *et al.*, D346591, 9-NOV-2007) and summary of analytical chemistry and residue data (W. Wassell and M. Sahafeyan, D340379, 9-AUG-2007).

## Summary

Difenoconazole is a broad-spectrum fungicide with registered seed-treatment uses on domestic cereal grains, canola and foreign rye, and foliar treatment on foreign banana and papaya, grapes, fruiting vegetables, pome fruit, sugar beets, tuberous and corm vegetables, in addition to ornamental use (homeowner application potential). Difenoconazole tolerances have been established in 40 CFR §180.475 (a) for plant and livestock commodities and are expressed in terms of difenoconazole *per se* for plants and difenoconazole + metabolite CGA-205375 for livestock commodities. The established tolerances for plant and livestock commodities range from 0.01 ppm (canola seed and various crops) to 4.5 ppm (apple, wet pomace). The ornamental use is the only potential residential application use.

## Hazard Assessment

The toxicological database for difenoconazole is adequate to support Section 18 registration on almonds. There are no toxicology data gaps (see previous human-health risk assessment document for details; Memo, Sahafeyan, *et al.*, 09-NOV-07; DP# 346591)

The toxicological doses relevant to this assessment are summarized below. It should be noted that a cancer dietary assessment was not conducted for difenoconazole because the cancer no-observable-adverse-effect-level (NOAEL) is higher than the chronic NOAEL; therefore, the chronic dietary risk estimate is more protective of any cancer effects.

Acute dietary (general population including infants and children)	NOAEL = 25 mg/kg/day	acute RfD <sup>3</sup> and acute population-adjusted dose (aPAD) = 0.25 mg/kg/day
Chronic dietary	NOAEL = 0.96 mg/kg/day	chronic RfD and cPAD <sup>4</sup> = 0.01 mg/kg/day
Short-term dermal <sup>1</sup>	oral NOAEL = 1.25 mg/kg/day	Target MOE <sup>5</sup> ≥ 100 (occupational and residential)
Short-term inhalation <sup>2</sup>	oral NOAEL = 1.25 mg/kg/day	Target MOE ≥ 100 (occupational and residential)
Incidental oral, short (1-30 days) and intermediate (1- 6months) term	NOAEL = 1.25 mg/kg/day	Target MOE ≥ 100

<sup>1</sup> Dermal-absorption factor = 15.3%

<sup>2</sup> Inhalation-absorption factor = 100%

<sup>3</sup> RfD = Reference Dose

<sup>4</sup> cPAD = chronic population-adjusted dose

<sup>5</sup> MOE = margin of exposure

### *Occupational Exposure and Risk Assessments*

(Reference: Memorandum, M. Dow, D351893, 5-MAY-2008)

No residential exposure is expected from the subject use (on almonds); ornamental foliar treatment remains the only potential residential use. For occupational exposure, given the comparatively small application area, no possibility of consecutive applications (as stated in the use directions), and the short treatment window (April to June), only short-term duration exposures (1-30 days) for occupational pesticide handlers are expected from the proposed use on almonds.

*Occupational-* A margin of exposure (MOE) of 100 is adequate to protect occupational pesticide handlers from exposures to difenoconazole. Provided occupational handlers wear protective gloves, all MOEs are >100; therefore, occupational exposures are not of concern to HED.

*Post-Application-* A MOE of 100 is adequate to protect agricultural workers from post-application exposures. The MOE is >100; therefore, the proposed use does not exceed HED's level of concern for post-application exposures.

### *Drinking Water*

(Reference: Memorandum, I. Maher, 19-JUN-2007, DP#333319)

The current use request is not expected to result in higher-level residues of difenoconazole in surface or ground water than the currently-registered uses; therefore, the previously-modeled estimated drinking water concentrations (EDWCs) from aerial applications of difenoconazole to California ornamental nurseries (the worst-case scenario) were used in the acute (**13.3 ppb**) and the chronic (**9.43 ppb**) dietary risk assessments (see Memo, I. Maher, 19-JUN-2007, DP#333319).

### *Dietary Exposure Estimates*

(Reference: Memorandum, M. Sahafeyan, D351961, 1-MAY-2008)

**Note:** While this document deals with the Section 18 emergency exemption on almonds only, a separate Section 18 document is being generated that deals with the use of difenoconazole on cucurbit crop group; however, only a single dietary risk assessment was conducted which included both requested uses.

Aggregate (food + water) acute and chronic dietary exposure and risk assessments were conducted using the Dietary Exposure Evaluation Model - Food Consumption Intake Database (DEEM-FCID™, ver. 2.03) model. This model uses food consumption data from the United States Department of Agriculture's (USDA's) Continuing Surveys of Food Intakes by Individuals (CSFII; 1994-1996 and 1998). The analyses were performed to support two Section 18 requests for the use of the fungicide difenoconazole in/on almonds and cucurbit crop group (group 9) with recommended time-limited tolerances of 0.05 ppm, 5.0 ppm, and 1.0 ppm for almond nutmeat, almond hulls, and the cucurbit crop group, respectively.

The unrefined (Tier 1) acute and chronic analyses assumed tolerance-level residues, 100% crop treated (CT), and empirical and DEEM™ (ver. 7.81) default processing factors for most commodities. The drinking water values used in the dietary risk assessment were provided by the Environmental Fate and Effects Division (EFED; Memo, I. Maher, 19-JUN-2007; DP# 333319). The resulting acute and chronic aggregate exposure estimates were not of concern to HED; the results are shown in Table 1.

*Acute Dietary (food + water) Exposure and Risk Assessment* - The resulting acute food and water exposure estimates were not of concern to HED (<100% of the acute population-adjusted dose (aPAD)) at the 95<sup>th</sup> percentile of the exposure distribution for U.S. general population (2.9% aPAD) and all population subgroups; the most highly exposed population subgroup was all-infants <1 year old with 9.0% aPAD.

*Chronic Dietary (food + water) Exposure and Risk Assessment* - The resulting chronic food and water exposure estimates were not of concern to HED (<100% of the chronic population-adjusted dose (cPAD)) for U.S. general population (23% cPAD) and all population sub-groups; the most highly exposed population subgroup was children 1-2 years old with 65% cPAD.

*Cancer Dietary Exposure and Risk Assessment* - A cancer dietary assessment was not conducted for difenoconazole because the cancer no-observable-adverse-effect-level (NOAEL) is higher than the chronic reference dose (RfD); therefore, the chronic dietary risk estimate is protective of any cancer effects.

*Triazoles Dietary Exposure and Risk Assessments* - The aggregate dietary (food + water) acute and chronic dietary exposure analyses for difenoconazole metabolites 1,2,4- triazole (1,2,4-T) and triazole alanine (TA) and triazole acetic acid (TAA) from all registered and proposed triazole-based fungicides uses already include exposure to almonds at higher-level exposures by other triazole-based fungicides and are not of concern (Memo, M. Doherty, DP#322238, 1-NOV-2005).

**Table 1.** Summary of Dietary (Food and Drinking Water) Exposure and Risk for Difenconazole.

Population Subgroup	Acute Dietary (95th Percentile)		Chronic Dietary	
	Dietary Exposure (mg/kg/day)	% aPAD	Dietary Exposure (mg/kg/day)	% cPAD
General U.S. Population	0.007277	2.9	0.002265	23
All Infants (< 1 year old)	<b>0.022518</b>	<b>9.0</b>	0.005586	56
Children 1-2 years old	0.019060	7.6	<b>0.006516</b>	<b>65</b>
Children 3-5 years old	0.016481	6.6	0.005547	56
Children 6-12 years old	0.009954	4.0	0.003287	33
Youth 13-19 years old	0.004989	2.0	0.001663	17
Adults 20-49 years old	0.004768	1.9	0.001632	16
Adults 50+ years old	0.005685	2.3	0.001880	19
Females 13-49 years old	0.004915	2.0	0.001637	16

*Aggregate Exposure Scenarios and Risk Conclusions*

(Updated from the previous risk assessment memorandum: M. Sahafeyan, *et al.*, 09-NOV-07; DP# 346591)

Based on the proposed and established uses, HED believes pesticide handlers (including residential handlers for ornamental foliar treatment) will be exposed to short-term duration (1-30 days) exposures, but not to intermediate-term (1-6 months) duration exposures. Moreover, since the short-term and intermediate-term toxicological endpoints are the same, the assessment of short-term exposure and risk is adequate to describe risk from an intermediate-term exposure, should that occurs.

Including all existing and proposed uses, human-health risk aggregate risk assessments have been conducted for the following exposure scenarios: chronic dietary exposures (food + water) + residential short-term exposure (dermal + inhalation). Since the aggregate MOEs are  $\geq 170$  short-term aggregate exposure to difenconazole is not of concern.

*Short-Term Aggregate Risk Assessment:* Since a common endpoint has been identified for assessment of short-term oral, dermal, and inhalation exposures (changes in body weights and body-weight gains) the short-term aggregate risk assessment considered exposure from food, water, and residential sources. Since the doses corresponding to the identified oral, dermal, and inhalation endpoints were different but the level of concern for all three routes of exposure is identical, the short-term aggregate exposures were calculated using the 1÷MOE approach. HED

combines chronic dietary (food and water) exposure estimates with residential exposure estimates when conducting short-term aggregate risk assessments. Short-term exposure has been defined as from 1-30 days and HED has concluded that chronic dietary exposure estimates will more accurately reflect actual dietary exposure over these time periods than will high-end acute-dietary exposures. The proposed residential scenarios result in exposure to only adults. Therefore, short-term aggregate assessments were not conducted for infants and children. Table 2 is a summary of the short-term aggregate exposures and risk estimates. Since the aggregate MOEs are  $\geq 170$ , short-term aggregate exposure to difenoconazole is not of concern to HED.

<b>Table 2. Short-Term Aggregate Exposure</b>				
Population	Target Aggregate MOE <sup>1</sup>	dietary MOE <sup>2</sup>	dermal + inhalation MOE <sup>3</sup>	agg. MOE (dietary and residential) <sup>4</sup>
Youth 13-19 years old	100	750	230	180
Adults 20-49 years old		770		180
Adults 50+ years old		660		170
Females 13-49 years old		760		180

<sup>1</sup> total uncertainty factor for all routes of exposure is 100x; therefore, the target MOE is 100.

<sup>2</sup> dietary MOE = short-term incidental oral NOAEL ÷ chronic dietary exposure.

<sup>3</sup> dermal and inhalation MOE = short-term dermal and inhalation NOAEL ÷ (dermal + inhalation residential exposure) (see memo, M. Sahafeyan, *et al.*, 09-NOV-07; DP# 346591).

<sup>4</sup> aggregate MOE (dietary and residential) =  $1 \div ((1 \div \text{MOE}_{\text{dietary}}) + (1 \div \text{MOE}_{\text{dermal + inhalation}}))$ .

### *Recommendation for Tolerances and Registration*

HED has no objection to the issuance of the Section 18 emergency exemption for the use of difenoconazole on almonds in California. To support this Section 18 use, Section 18 emergency exemption tolerances for residues of difenoconazole *per se* should be established as follows:

Crop (commodity)	Tolerance Level (ppm)
Almond	0.05
Almond, hulls	5.0

## Detailed Discussion

### Use Directions

The use pattern summary is taken from the California Section 18 request (California ID # 226122; A. Yokoyama Cal. Dept. Pestic. Reg. 11 APRIL 2008). The product requested for use is Inspire™ Super TM Fungicide (EPA Reg. No. 100-1262) produced by Syngenta Crop Protection. Inspire™ is formulated as a 23.2 %, 2.08 lb ai/gal liquid. The rate of application is 7 fl oz product/acre (A) (0.11 lb ai/A). It is to be applied by ground air-blast sprayer in a maximum of 300 gal of water/A. Applications will be made from 15 April to 30 June with a maximum of 2 applications. Applications may not be consecutive. A retreatment interval is not stated. A maximum of 145,000 acres may be treated (145,000 A \* 0.11 lb ai/A = 15,950 total lb ai or 31,900 lb ai if 2 applications/A are made). The PHI is 30 days and the restricted-entry interval (REI) is 12 hours.

### Magnitude of the Residues

The Interregional Research Project No. 4 (IR-4) has submitted preliminary (only) data from five field trials conducted in Region 12 (State of California) in which four foliar applications of EC 250 (unregistered formulation, contains 25% difenoconazole) were made at the rate of 0.11 lb a.i./A with 14-day PHI at different volume ranges (9-400 gallons per acre, GPA); this rate is twice the proposed total application rate with a PHI of about half the one proposed. These data are summarized in Table 3.

Location, Year	Commodity	Application rate (lb ai/A)	No. of Application	Total rate (lb ai/A)	PHI (days)	Difenconazole residues (ppm)
Parlier, CA/2006	nutmeat	0.11	4	0.44	14	<0.05 <sup>1</sup> , <0.05 <sup>1</sup>
	hulls					1.20 <sup>1</sup> , 1.23 <sup>1</sup>
Parlier, CA/2006	nutmeat					<0.05 <sup>2</sup> , <0.05 <sup>2</sup>
	hulls					2.78 <sup>2</sup> , 2.15 <sup>2</sup>
Parlier, CA/2006	nutmeat					<0.05 <sup>3</sup> , <0.05 <sup>3</sup>
	hulls					3.03 <sup>3</sup> , 2.05 <sup>3</sup>
Davis, CA/2006	nutmeat					<0.05, <0.05
	hulls					1.13 <sup>3</sup> , 1.06 <sup>3</sup>
Davis, CA/2006	nutmeat					<0.05 <sup>3</sup> , <0.05 <sup>3</sup>
	nutmeat					<0.05 <sup>3</sup> , <0.05 <sup>3</sup>
	hulls					0.78 <sup>3</sup> , 0.63 <sup>3</sup>
	hulls					0.62 <sup>3</sup> , 0.68 <sup>3</sup>

<sup>1</sup>Spray Range = 9-11 Gallons Per Acre (GPA)

<sup>2</sup>Spray Range = 50-100 GPA

<sup>3</sup>Spray Range = 101-400 GPA

HED concludes that difenoconazole residues in/on almond and almond hulls from the proposed use rate should not exceed 0.05 ppm and 5.0 ppm, respectively. These tolerance levels are as per California DPR's recommendation and were determined using the *Guidance for Setting Pesticide*



*Tolerances Based on Field Trial Data (SOP) along with the tolerance spreadsheet.*

### Processed Commodities

There are no processed commodities associated with almonds for which residue data are required.

### Meat, Milk, Poultry and Eggs

As almond hulls is considered a dairy cattle feed item, a new dairy cattle diet based on the proposed (almond hulls) and registered uses of difenoconazole and according to the revision of feedstuffs in OPPTS 860.1000 Table 1 referenced as "Table 1 Feedstuffs (April 2008)" was constructed; see Table 4 below.

<b>Table 4. Calculation of Dietary Burdens of Difenconazole Residues for Dairy Cattle.</b>					
Feedstuff	Type <sup>1</sup>	% Dry Matter <sup>2</sup>	% Diet <sup>2</sup>	Established/Recommended Tolerance (ppm)	Dietary Contribution (ppm) <sup>3</sup>
<b>Dairy Cattle</b>					
Almond hulls <sup>4</sup>	R	90	10	5.0	0.55
Wheat, forage	R	25	30	0.10	0.12
Corn, sweet, forage	R	48	5	0.01	0.001
Barley, grain	CC	88	10	0.1	0.011
Wheat, grain/milled byproducts	CC	88	35	0.10	0.040
Cotton seed, meal	PC	89	10	0.05	0.006
<b>TOTAL BURDEN</b>	--	--	100	--	<b>0.73</b>

<sup>1</sup> R: Roughage; CC: Carbohydrate concentrate; PC: Protein concentrate.

<sup>2</sup> Revision of feedstuffs in OPPTS 860.1000 Table 1 referenced as "Table 1 Feedstuffs (April 2008)".

<sup>3</sup> Contribution = ([tolerance /% DM] X % diet) for beef and dairy cattle

<sup>4</sup> As almond hulls and apple wet pomace are considered esoteric feedstuff and it has been a general practice to include only one esoteric feedstuff in livestock diets (ChemSAC minutes, dated 12/17/03), apple wet pomace (used previously in constructing cattle diet) was not included in the dietary burden.

The new dietary burden from Table 4 above (0.73 ppm) is lower than the previously-calculated dietary burden (1.3 ppm; see W. Wassell and M. Sahafeyan, D340379, 8/9/08) due to the fact that two esoteric feedstuff (almond hulls and apple wet pomace) are not generally fed simultaneously to the livestock (see Table note 4). Therefore, the currently-established tolerances on beef/dairy cattle tissues are still sufficient.

### Rotational Crop Restrictions

No rotational crop restriction requirement is applicable since almond groves are not rotated.

### International Residue Limits

There are no Codex maximum residue limits (MRLs) established for difenoconazole on almonds (see Attachment 1). Therefore, no compatibility problems exist for the proposed tolerances.

Petition Number: 08CA12

DP#: 351715

PC Code: 128847

M. Sahafeyan: S10944:PY1:(703)-305-0776

Attachment 1: International Residue Limit Status (IRLS) Sheet

## ATTACHMENT 1: IRLS Sheet

INTERNATIONAL RESIDUE LIMIT STATUS			
Chemical Name: 1-[[2-[2-chloro-4-(4-chlorophenoxy)phenyl]-4-methyl-1,3-dioxolan-2-yl]methyl]-1H-1,2,4-triazole	Common Name: Difenoconazole	Proposed tolerance Reevaluated tolerance X Other : Section 18 emergency exemption	Date: 5/1/08
Codex Status (Maximum Residue Limits)		U. S. Tolerances	
No Codex proposal step 6 or above ✓ No Codex proposal step 6 or above for the crops requested		Petition Number: NA (Section 18, 08CA12) DP#: 351715 Other Identifier: Decision Number 392318	
Residue definition (step 8/CXL): difenoconazole		Reviewer/Branch: M. Sahafeyan / RAB1	
		Residue definition: Difenoconazole <i>per se</i>	
Crop (s)	MRL (mg/kg)	Crop(s)	Tolerance (ppm)
		Almond, nutmeat	0.05
		Almond, hulls	5.0
Limits for Canada		Limits for Mexico	
No Limits ✓ No Limits for the crops requested		No Limits ✓ No Limits for the crops requested	
Residue definition: 1-[2-[4-(4-chlorophenoxy)-2-chlorophenyl]-4-methyl-1,3-dioxolan-2-ylmethyl]-1H-1,2,4-triazole		Residue definition: difenoconazole	
Crop(s)	MRL (mg/kg)	Crop(s)	MRL (mg/kg)
Notes/Special Instructions: S. Funk, 05/06/2008.			



13544

# R159266

**Chemical Name:** Difenoconazole

**PC Code:** 128847

**HED File Code:** 14000 Risk Reviews

**Memo Date:** 5/7/2008

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